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Ibrutinib, lenalidomide, and rituximab in relapsed mantle cell lymphoma: Long-term follow-up of the Nordic Lymphoma Group MCL6 Philemon trial

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Graphical Abstract

2015-2016

- 50 patients with R/R MCL
- Ibrutinib, lenalidomide, rituximab
- Overall response: 86%
- Baseline health-related quality of life

Long-term follow-up | Comparison with the population-based register *MCL* complete

2023

- Median progression-free survival: 17.4 months
- 28% relapse-free at 5 years
- High response in *TP53* mutated patients, but a trend towards poorer long-term outcome
- Lower global quality of health associated with impaired overall survival
- Superior survival compared to a matched population-based cohort

A bridge towards allogeneic stem cell transplantation and CAR-T therapy ?

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Ibrutinib, lenalidomide, and rituximab in relapsed mantle cell lymphoma: Long-term follow-up of the Nordic Lymphoma Group MCL6 Philemon trial

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Abstract

Relapsed or refractory mantle cell lymphoma (R/R MCL) remains difficult to treat, with outcomes dependent on the treatment regimen and remission duration after first-line therapy. Several non-chemotherapeutic regimens are under evaluation in R/R, but few studies report long-term outcomes. In this study, we present the long-term outcomes of the 50 patients treated with ibrutinib, lenalidomide, and rituximab (IR2) in the Nordic Lymphoma Group MCL6 Philemon phase 2 trial. Survival outcomes were compared with a matched cohort from the Swedish MCL*complete* study. After 5 years, 14 patients (28%) remained relapse-free, including one with a *TP53* mutation. The median progression-free survival (PFS) was 17.4 months, with the longest PFS of 8.1 years. Thirty-two patients had died, primarily from MCL (72%). Poorer survival was associated with intermediate or high-risk Mantle Cell Lymphoma International Prognostic Index and impaired health-related quality of life (HRQoL). While *TP53* mutations ($n = 11$) did not significantly impact survival, a trend toward poorer outcomes was observed in multivariable Cox regression analyses (PFS hazard ratio: 2.09, 95% confidence interval: 0.95–4.62, $p = 0.068$). The IR2 regimen demonstrated superior survival compared to the MCL*complete* cohort both before and after matching. In conclusion, this study highlights the role of non-chemotherapeutic agents in R/R MCL and demonstrates the prognostic impact of HRQoL on overall survival. Although IR2 showed initial activity in TP53-mutated patients, it did not completely overcome their poor prognosis. However, the IR2 regimen may serve as a bridge to allogeneic stem cell transplantation or chimeric antigen receptor T-cell therapy.

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INTRODUCTION

Mantle cell lymphoma (MCL) is a rare, aggressive B-cell lymphoma associated with poor survival outcomes due to frequent relapses. For patients with relapsed or refractory (R/R) MCL, there is limited consensus on the optimal treatment options, and the prognosis remains particularly poor for those with *TP53* mutations.[1,2] Therefore, clinical studies investigating novel treatment regimens in R/R MCL are vital to improve survival outcomes. As the overall survival (OS) in MCL is improving, with an increasing number of new drugs available, it is also important to assess long-term survival outcomes and potential late effects arising from new treatment regimens.

Currently, the treatment landscape for MCL is shifting from chemoimmunotherapy to targeted therapies and cellular approaches, including chimeric antigen receptor (CAR) T-cell therapy[1,3] and bispecific antibodies.[4,5] For these novel non-chemotherapeutic drugs, various treatment regimens are currently being tested, both as monotherapy and in combination. Many new combination therapies are developed with Bruton's tyrosine kinase (BTK) inhibitor backbone, such as ibrutinib,[6] acalabrutinib,[7] and zanubrutinib.[8] Ibrutinib, the first-in-class covalent BTK inhibitor, has become a cornerstone in the treatment of R/R MCL, achieving response rates between 68% and 70%.[9–11] Lenalidomide is another non-chemotherapeutic drug that in combination with the CD20-antibody rituximab has shown activity in MCL treatment and has been evaluated in both frontline and relapsed settings.[12,13] Lenalidomide is an immunomodulatory agent with antiangiogenic and antineoplastic properties. It promotes the proliferation and activation of natural killer (NK) cells, thereby enhancing the cytotoxicity mediated by NK cells and working as an immunosensitizer.[14] A combination of ibrutinib, lenalidomide, and rituximab (IR2) was speculated to exhibit a synergistic effect and was evaluated in the Nordic Lymphoma Group MCL6 Philemon, a multicenter, single-arm, phase 2 trial. The first read-out of the trial showed an overall response rate (ORR) of 86% (95% confidence interval [CI] 73.3–93.6) and activity in patients with *TP53* mutated disease.[15] However, the long-term survival and late adverse effects of this regimen are still unknown.

In this follow-up study, we present the long-term outcomes of the IR2 regimen and compare the observed survival to that of a matched Swedish population-based cohort, MCL*complete*. Additionally, we assess the prognostic impact of health-related quality of life (HRQoL) in R/R MCL and describe long-term adverse side effects.

MATERIALS AND METHODS

Study design in Philemon

Philemon was an open-label, multi-center phase 2 trial, conducted by the Nordic Lymphoma Group. Fifty patients with R/R MCL from 10 centers in Sweden, Finland, Norway, and Denmark were included between January 1, 2015 and June 5, 2016. Inclusion criteria were age 18 years or older, an MCL diagnosis, previous treatment with at least one rituximab-containing regimen, and an Eastern Cooperative Oncology Group (ECOG) performance status score of 0–3. Exclusion criteria were central nervous system involvement, human immunodeficiency virus infection, active hepatitis B or C infection, stroke, or intracranial hemorrhage (within 6 months before enrollment), need for anticoagulation with warfarin (or equivalent vitamin K antagonist), or treatment with strong or moderate CYP3A inhibitors. Previous treatment with ibrutinib or lenalidomide was allowed.[15]

IR2 treatment

The treatment consisted of an induction phase of 12 months, including all three agents, and a maintenance phase with ibrutinib and rituximab, both given until progression or unacceptable toxicity, with a cycle length of 28 days. Ibrutinib was administrated orally at 560 mg/day and lenalidomide orally at 15 mg/day on days 1–21. Rituximab was given once weekly for 4 weeks during cycle 1, then every 8 weeks.[15] Adverse events were assessed according to the Common Toxicity Criteria for Adverse Events (CTCAE) version 4.03. The response rate was assessed according to the Lugano criteria, with bone marrow examinations as well as a positron emission tomography to confirm complete response or at the time of maximal tumor regression.[15]

Genetic analyses

DNA from bone marrow samples was examined for mutations in coding regions, splice sites, and untranslated regions in the *TP53* gene, using the Ion Torrent technology, as described previously.[2]

Quality of life (QoL)

To assess HRQoL, we used the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire. It encompasses five functional scales—physical, emotional, cognitive, role, and social functioning—as well as three symptom scales focusing on fatigue, pain, and nausea/vomiting. Additionally, it evaluates global health status and includes single-item measures such as dyspnea, appetite loss, insomnia, constipation, diarrhea, and the financial impact of the disease.[16]

Long-term follow-up and endpoints

A new electronic case report form (CRF) was created and sent to all investigators at the 10 study sites. The CRF included the time of the last follow-up (last date available in medical records), occurrence of relapse or death, cause of death, information on further treatment, and new response evaluations. No data on continuous treatment were available. In addition, data on severe late effects and secondary malignancies were collected. The primary endpoints were progression-free survival (PFS) and OS. Secondary endpoints were response rate and late adverse events. All CRFs were completed in December 2023.

MCL*complete*

MCL*complete* is a population-based patient cohort from Sweden.[17] Patients diagnosed between 2006 and 2018 and registered in the nationwide Swedish lymphoma register (SLR) were included.[18] The SLR has high coverage and encompasses approximately 95% of all lymphoma cases in Sweden.[19] To retrieve additional information regarding response to first-line treatment and relapse, retrospective reviews of medical records were performed. In total, MCL*complete* included 1418 MCL patients, and the most common treatment was chemotherapy (92.7%). All patients had received rituximab. To facilitate a proper comparison with the trial population, patients with their first relapse after last inclusion date in Philemon (June 5, 2016) were excluded ($n = 1035$). Additionally, 63 patients lacked information on the Mantle Cell Lymphoma International Prognostic Index (MIPI) category as a continuous variable, resulting in a refined cohort of 320 patients (Figure S1).

Ethics

The study received approval from the respective national ethics committees in the four countries and was conducted in alignment with the Declaration of Helsinki and the International Conference on Harmonization guidelines for Good Clinical Practice. Written informed consent was obtained from all patients. The trial was registered on clinicaltrials.gov (NCT02460276). For the comparison with MCL*complete*, the study was approved by the Regional Board of the Ethical Committee in Lund, Sweden (2018/739).

Statistics

To evaluate survival outcomes, the Kaplan–Meier estimator was used to estimate OS and PFS, and the log-rank test was applied to test survival differences. In the Philemon cohort, OS was defined as time from inclusion date to death or censoring and PFS as time from inclusion to next relapse, death, or censoring. Duration of response (DOR) was calculated from the date of best response (complete or partial) to the date of progression. In the MCL*complete* cohort, OS was defined as the time from the last relapse before June 5, 2016, to death or censoring, and PFS as the time from last relapse before June 5, 2016, to the next relapse, death, or censoring.

Exploratory analysis

In the Philemon cohort, OS and PFS were stratified by sex, MIPI, and *TP53* mutation status. Univariable and multivariable regression analyses were performed adjusting for MIPI, *TP53* mutation status, previous number of treatment lines, and, if significant, scales in HRQOL. HRQOL was stratified and calculated according to the EORTC QLQ-C30 manual.[20] The scales were stratified above or below median.

To compare survival differences between the population-based MCL*complete* and Philemon, a hybrid matching technique according to Mahalanobis distance was used, including exact 1:1 matching on the MIPI category and the number of prior lines of treatment, grouped as 1, 2–3, and ≥4. To quantify the absolute effect of treatment, PFS and OS were assessed using the restricted mean survival time (RMST), defined as the area under the survival curve. The RMST differences were calculated at 1, 2, and 5 years since the last relapse. At each time point, the level of significance was evaluated by Wald tests, and 95% CI were determined by pooling standard errors. As three patients had withdrawn consent, sensory analyses were performed.

All analyses were performed using R 4.2.3 in RStudio (version 2023.03.02). The matching was performed using the MatchIt package,[21] and RMS was calculated using the SurvRM2 package.[22] The survival package was used to calculate OS and PFS.[23]

RESULTS

Differences in patient characteristics between Philemon and MCL*complete*

A total of 50 patients were included in the Philemon cohort and 320 patients in the MCL*complete* cohort (Table 1). In the Philemon cohort, 11 (22%) had a *TP53* mutation. Four (8.0%) patients in Philemon had previously been treated with ibrutinib, and in MCL*complete* only six patients (1.6%). As data on previous lines of treatment were missing in two patients, 48 patients in Philemon were matched to 48 patients in MCL*complete*. Before matching, age and MIPI distribution were similar between the groups, but the absolute standard mean (ASM) difference was highest in sex and Ann Arbor stage, although not prominent (Table 1). The ASM diminished in all categories after the matching 1:1 procedure, besides a slight increase in Ann Arbor stage and ECOG, indicating acceptable matches (Table 1 and Figure S2).

Survival outcomes for patients treated with IR2

In the Philemon cohort, the median follow-up time (calculated with reverse Kaplan–Meier[24]) is currently 92 months (inter quartile range [IQR]: 88.2–96.9) with a median PFS of 17.4 months (IQR: 5.3–80.5) and a median OS of 45.3 months (IQR: 11.3 to NA) (Figure 1). The longest PFS observed was 8.1 years. The 1-year PFS was 62% (95% CI: 0.61–0.86) (Table 2), and the median DOR was 39.9 months (IQR 10.0 to NA) (Figure 1). Of the four patients with previous ibrutinib exposure, two patients had a partial response, and the other two had progressive disease. The two patients responding had DOR of 2.3 months and 3.2 years, respectively. When examining patients with *TP53* mutation ($n = 11$), the 1-year PFS was 55% (95 CI: 0.32–0.94) (Table 2), and the ORR was 79% (Table S1). One patient with *TP53* mutation was still relapse-free at the end of follow-up, with a PFS of 7.3 years. However, this patient had undergone an allogeneic stem cell transplantation immediately after the IR2 regimen. For the *TP53* mutated patients, the survival estimates were borderline significant compared to patients without the mutation, showing a trend toward an inferior outcome (OS, $p = 0.09$; PFS, $p = 0.13$) (Figure 2). In both univariable and multivariable Cox regression analyses (adjusted for sex, MIPI, QoL, and previous lines of treatment), *TP53* mutation status was not significantly associated with prognosis neither in PFS nor OS. However, there was a trend toward a higher hazard for progression in patients with the mutation (PFS hazard ratio [HR]: 2.09, 95% CI: 0.95–4.62, $p = 0.068$) (Tables S2 and 3). This suggests that the IR2 regimen had initial activity in *TP53* mutated patients, but was unable to fully overcome the poor prognostic outlook.

When comparing OS rates in the Philemon cohort, we found that disease characteristics associated with inferior outcomes were high- and intermediate-risk MIPI, a global health status/QoL below median, and more than one previous line of treatment (Figure 3). However, in the log rank test and univariable analyses, only intermediate or high-risk MIPI ($p = 0.041$) compared to low-risk MIPI and QoL below median ($p = 0.016$) were significant (Figure 3 and Table S2). This inferior outcome was also significant in both univariable and multivariable Cox regression models adjusting for sex, *TP53* mutation and previous lines of treatment (QoL hazard ratio [HR]: 2.53; 95% CI: 2.53–5.80, $p = 0.028$) (Table 3). When stratified by previous lines of treatments, there was no significant difference in PFS between patients receiving more than one line or one line of previous therapies ($p = 0.18$) (Figure 3F), nor adjusted for sex, MIPI, *TP53* mutation status, and QoL (Table 3). When examining QoL, patients with QoL below the median tended to be slightly older, have a higher MIPI score, and a lower Ann Arbor stage. However, none of these differences were statistically significant (Table S3). In contrast, QoL was not significant for PFS, suggesting that this variable is more correlated to OS rather than predicting the PFS after treatment in a relapsed setting.

HRQoL

The medians of each functioning and symptomatic scale are summarized in Table 4, and the distribution in each scale is shown in Figure S3.

TABLE 1 Patient characteristics in Philemon and MCL*complete* with differences calculated by absolute standardized mean difference before and after matching.

Patient characteristics	Philemon, *N* = 50 (%)	MCL*complete* unmatched, *N* = 320 (%)	Absolute standardized mean difference	Philemon, *N* = 48 (%)	MCL*complete*, matched, *N* = 48 (%)	Absolute standardized mean difference
Age	70 (45–85)[a]	71 (36–91)[a]	0.215[b]	70 (45–85)[a]	69 (45–85)[a]	0.088[b]
Sex						
Female	14 (28)	65 (20)	0.152	13 (27)	12 (27)	0.00
Male	36 (72)	255 (80)	0.152	35 (73)	33 (73)	0.00
Ki67 proliferation index[c]						
Ki67 < 30	16 (40)					
Ki67 ≥ 30	24 (60)					
TP53 mutation[c]						
Yes	11 (22)					
No	38 (76)					
MIPI			0.086[b]			0.089[b]
Low risk	9 (18)	46 (14)	0.007	7 (15)	7 (15)	0.00
Intermediate risk	17 (34)	110 (34)	0.021	17 (35)	17 (35)	0.00
High risk	24 (48)	164 (51)	0.025	24 (50)	24 (50)	0.00
ECOG						
0	28 (56)	176 (55)	0.017	25 (50)	29 (60)	0.167
1	17 (34)	106 (33)	0.048	17 (35)	12 (25)	0.218
2	5 (10)	22 (6.9)	0.116	5 (10)	6 (13)	0.068
3	0 (0)	9 (2.8)	0.182	0 (0)	1 (2.1)	0.135
Missing	0 (0)	7 (2.2)	0.160	0 (0)	1 (2.1)	0.153
Ann Arbor stage						
1	0 (0)	15 (4.7)	0.238	0 (0)	4 (8.3)	0.211
2	0 (0)	30 (9.4)	0.345	0 (0)	4 (8.3)	0.307
3	8 (16)	42 (13)	0.095	8 (17)	7 (15)	0.112
4	42 (84)	225 (70)	0.345	40 (83)	32 (67)	0.335
Missing	0 (0)	8 (2.5)	0.172	0 (0)	1 (2.1)	0.286
Previous LOT			0.043[b]			0.110[b]
1	25 (50)	146 (46)		25 (52)	25 (52)	
2	9 (18)	78 (24)		9 (19)	9 (19)	
3	7 (14)	40 (12)		7 (15)	7 (15)	
4	2 (4.0)	56 (18)		2 (4.2)	7 (15)	
5	3 (6)	0 (0)		3 (6.3)	0 (0)	
6	1 (2.0)	0 (0)		1 (2.1)	0 (0)	
7	1 (2.0)	0 (0)		1 (2.1)	0 (0)	
Missing	2 (4)	0 (0)		0 (0)	0 (0)	
Previous LOT by group						
1	25 (52)	146 (46)	0.129	25 (52)	25 (52)	0.00
2–3	16 (33)	118 (37)	0.075	16 (33)	16 (33)	0.00
≥4	7 (15)	55 (18)	0.082	7 (15)	7 (15)	0.00
Previous Ibrutinib[c]						
Yes	4 (8)	6 (1.6)		4 (8)	1 (2)	
No	44 (92)	313 (98)		44 (92)	47 (98)	
Missing	0 (0)	1 (0.3)		0 (0)	0 (0)	

Abbreviations: ECOG, Eastern Cooperative Oncology Group; LOT, lines of treatment; MIPI, Mantle Cell Lymphoma International Prognostic Index.

[a]Median (range).

[b]Absolute standardized mean difference calculated in continuous form.

[c]Not a matching variable.

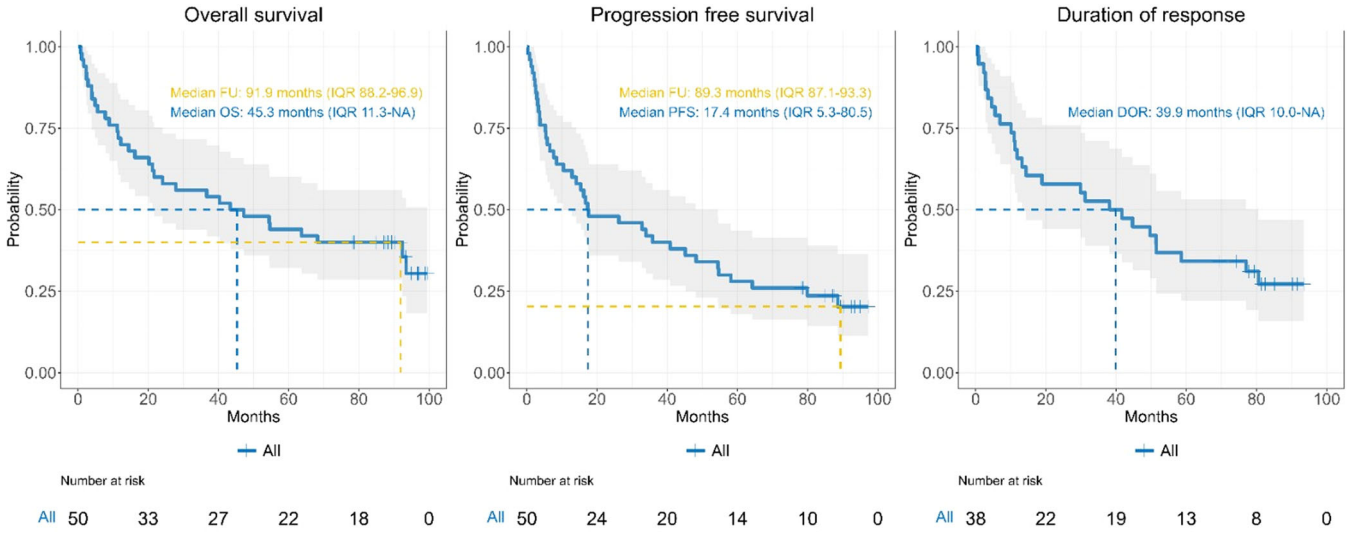

FIGURE 1 Kaplan–Meier estimates and the median follow-up time of overall survival and progression-free survival in the Philemon cohort.

TABLE 2 One-, two- and five-year survival estimates in Philemon, overall and progression-free survival.

Covariate	Survival 1 year (95% CI)	Survival 2 years (95% CI)	Survival 5 years (95% CI)
Overall survival Philemon			
All	0.72 (0.61, 0.86)	0.60 (0.48, 0.75)	0.44 (0.32, 0.60)
Female	0.64 (0.44, 0.95)	0.50 (0.30, 0.84)	0.43 (0.23, 0.79)
Male	0.75 (0.62, 0.91)	0.64 (0.50, 0.82)	0.44 (0.31, 0.64)
MIPI high risk	0.67 (0.50, 0.89)	0.54 (0.38, 0.78)	0.38 (0.22, 0.63)
MIPI intermediate risk	0.70 (0.52, 0.96)	0.53 (0.34, 0.83)	0.35 (0.19, 0.67)
MIPI low risk	0.89 (0.71, 1.00)	0.89 (0.71, 1.00)	0.78 (0.56, 1.00)
Ki67 < 30	0.67 (0.49, 0.96)	0.63 (0.43, 0.91)	0.56 (0.37, 0.87)
Ki67 ≥ 30	0.67 (0.50, 0.86)	0.54 (0.38, 0.78)	0.42 (0.26, 0.70)
TP53 unmutated	0.76 (0.64, 0.91)	0.66 (0.52, 0.83)	0.50 (0.36, 0.69)
TP53 mutated	0.64 (0.41, 1.00)	0.46 (0.24, 0.87)	0.28 (0.10, 0.72)
Progression-free survival Philemon			
All	0.62 (0.50, 0.77)	0.48 (0.36, 0.64)	0.28 (0.18, 0.44)
Female	0.57 (0.36, 0.90)	0.50 (0.30, 0.84)	0.36 (0.18, 0.72)
Male	0.64 (0.50, 0.82)	0.47 (0.33, 0.67)	0.25 (0.14, 0.44)
MIPI high risk	0.50 (0.34, 0.75)	0.33 (0.19, 0.59)	0.25 (0.12, 0.50)
MIPI intermediate risk	0.65 (0.46, 0.91)	0.47 (0.28, 0.78)	0.24 (0.10, 0.55)
MIPI low risk	0.89 (0.70, 1.00)	0.89 (0.70, 1.00)	0.44 (0.21, 0.92)
Ki67 < 30	0.63 (0.43, 0.91)	0.56 (0.37, 0.87)	0.44 (0.25, 0.76)
Ki67 ≥ 30	0.50 (0.34, 0.75)	0.38 (0.22, 0.63)	0.21 (0.10, 0.45)
TP53 unmutated	0.66 (0.52, 0.83)	0.55 (0.42, 0.74)	0.34 (0.22, 0.53)
TP53 mutated	0.55 (0.32, 0.94)	0.27 (0.10, 0.72)	0.09 (0.01, 0.59)

Abbreviation: MIPI, Mantle Cell Lymphoma International Prognostic Index.

In univariable Cox regression analyses, patients with a score below median in QoL, emotional function, cognitive functioning, fatigue, and pain had a significantly worse OS. However, neither of these scores was significantly associated with PFS (Table 4).

Comparisons to MCL*complete*

To determine the survival differences before and after matching, we compared 48 patients receiving the IR2 regimen in Philemon to patients in the population-based MCL*complete* using survival estimates and RMST differences. In addition, the 1-, 2-, and 5-year survival estimates are shown in Table S4. Patients receiving IR2 exhibited superior survival compared to patients in MCL*complete*, both before and after matching (Figure 4). In unmatched analysis, the 5-year PFS RMST difference was 1.10 (95% CI: 0.49–1.72), $p < 0.01$) in favor of the Philemon cohort (Table 5). After matching, significance was retained with a 5-year PFS RMST difference of 1.15 (95% CI: 0.36–1.91, $p < 0.01$), indicating a more favorable long-term outcome for patients receiving the IR2 regimen. The results remained robust regardless of the inclusion or exclusion of the three patients who withdrew consent (Table S5).

Treatment at relapse post-IR2 in the Philemon cohort

Thirty-one patients had progression after IR2, and 23 patients received subsequent treatment (Figure S1). Most of the patients received rituximab–bendamustine ($n = 5$ [21%]), radiotherapy only ($n = 5$ [21%]), and a venetoclax regimen ($n = 5$ [21%]) (Table 6). For patients retreated post-IR2 ($n = 23$), the OS, calculated from the start of the first treatment after IR2 to the date of death or the date of the last follow-up, was 9.3 months (95% CI: 5.9 to NA). In the context of patients with *TP53* mutations, two patients underwent retreatment following the IR2 regimen. One patient received venetoclax in combination with lenalidomide and rituximab 3 years after the IR2 regimen, followed by CAR-T therapy. The other patient underwent multiple subsequent treatments, including acalabrutinib, rituximab, and bendamustine, as well as venetoklax and obinutuzumab. This patient died 3 years after enrollment in the Philemon study.

Long-term survival, late effects, and secondary malignancies

In December 2023, 11 patients were still relapse-free at the end of follow-up. Thirty-two patients had died, and the majority of them were in MCL ($n = 23$ [72%]) (Figure S1). Twenty-five patients were

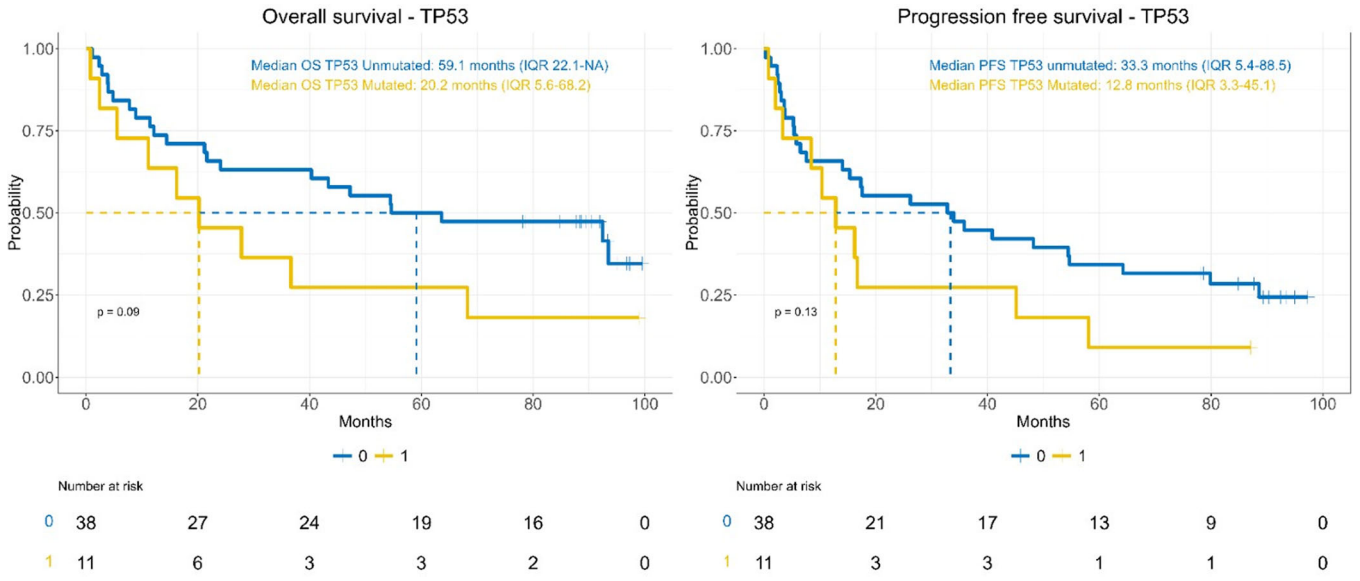

FIGURE 2 **Kaplan–Meier estimates of overall and progression-free survival, stratified by TP53 mutation.**

TABLE 3 Multivariable Cox regression models of overall and progression-free survival, adjusted for sex, MIPI category, *TP53* mutation, global health status, and previous lines of treatment.

	Overall survival				Progression-free survival		
Characteristic	***N***	**HR**	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**
Sex	47						
Female		—	—		—	—	
Male		1.10	0.47, 2.58	0.8	1.35	0.64, 2.84	0.4
MIPI category	47						
Low risk		—	—		—	—	
Intermediate risk		8.49	1.05, 68.6	**0.045**	3.13	0.99, 9.90	0.052
High risk		7.31	0.93, 57.6	0.059	2.75	0.89, 8.53	0.079
TP53 mutation	47						
No		—	—		—	—	
Yes		2.09	0.87, 5.03	0.10	2.09	0.95, 4.62	0.068
Global health status (QoL)	47						
Above Median		—	—		—	—	
Below Median		2.53	1.11, 5.80	**0.028**	1.17	0.59, 2.32	0.6
Previous lines of treatment	47						
1		—	—		—	—	
>1		1.99	0.90, 4.38	0.088	1.54	0.80, 2.99	0.2

Note: Three patients were excluded from the analysis due to missing data. Significant values ($p < 0.05$) are in bold.

Abbreviations: CI, confidence interval; HR, hazard ratio; MIPI, Mantle Cell Lymphoma International Prognostic Index.

available for evaluation of late effects since 22 patients had died at previous evaluation and three had withdrawn consent. Follow-up data from all 25 patients were retrieved. Eleven patients experienced long-lasting severe adverse effects, where polyneuropathy ($n = 4$) and hypogammaglobulinemia ($n = 2$) were the most common. Six patients had been diagnosed with a second malignancy: two patients with prostate cancer, one patient with basal cell carcinoma, one patient with non-small cell lung cancer, one patient with rectal cancer, and one patient with carcinoma in situ non-specified.

DISCUSSION

In this long-term follow-up of the Nordic Lymphoma Group Phase 2 Philemon trial, we found that patients treated with the IR2 regimen achieved durable responses, and superior survival compared to patients with R/R MCL in the population-based MCL*complete* cohort, both before and after matching. In addition, the regimen had initial efficacy in patients with *TP53* mutation, with high response rates, and median PFS exceeding 1 year. However, the IR2 regimen could not completely overcome the negative prognostic impact of the mutation.

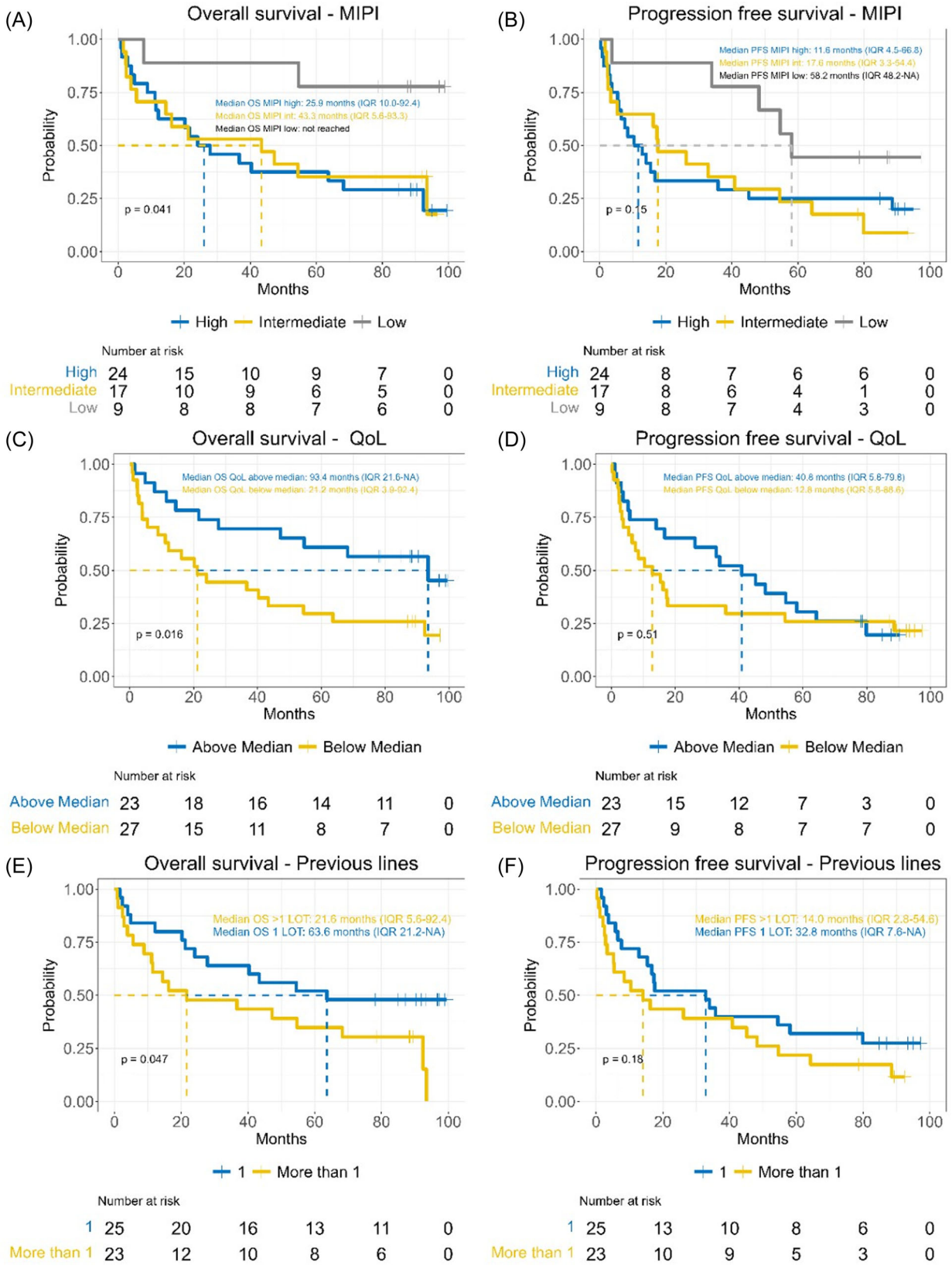

FIGURE 3 Kaplan–Meier estimates of overall and progression-free survival, stratified by (A, B) MIPI, (C, D) global health status/QoL, and (E, F) previous lines of treatment.

TABLE 4 Univariable Cox regression analyses of overall survival and progression-free survival for baseline health-related quality of life (HRQoL), stratified by each scale according to the QLQ-30 EORTC manual. (continued on next page)

Characteristic		N (%)	OS			PFS		
			HR	95% CI	p value	HR	95% CI	p value
Global quality of life/QoL	Median (IQR)	67 (42, 83)						
	Above median	23 (46)	–	–		–	–	
	Below median	27 (54)	2.40	1.15, 5.00	0.020	1.24	0.65, 2.34	0.51
Physical functioning	Median (IQR)	80 (67, 100)						
	Above median	24 (48)	–	–		–	–	
	Below median	26 (52)	1.75	0.86, 3.55	0.12	0.91	0.48, 1.71	0.76
Role functioning	Median (IQR)	67 (50, 100)						
	Above median	23 (46)	–	–		–	–	
	Below median	27 (54)	1.88	0.91, 3.89	0.088	0.88	0.47, 1.65	0.68
Emotional functioning	Median (IQR)	83 (69, 98)						
	Above median	20 (40)	–	–		–	–	
	Below median	30 (60)	2.19	1.01, 4.74	**0.046**	1.20	0.63, 2.29	0.57
Cognitive functioning	Median (IQR)	83 (67, 100)						
	Above median	23 (46)	–	–		–	–	
	Below median	27 (54)	3.06	1.39, 6.74	**0.006**	1.57	0.83, 2.99	0.17
Social functioning	Median (IQR)	83 (67, 100)						
	Above median	24 (48)	–	–		–	–	
	Below median	26 (52)	1.91	0.92, 3.96	0.082	0.90	0.48, 1.69	0.75
Fatigue	Median (IQR)	33 (22, 56)						
	Above median	22 (44)	–	–		–	–	
	Below median	28 (56)	0.45	0.22, 0.92	**0.027**	0.90	0.47, 1.70	0.74
Nausea and vomiting	Median (IQR)	0 (0, 0)						
	Above median	12 (24)	–	–		–	–	
	Below median	38 (76)	0.78	0.35, 1.74	0.54	1.17	0.54, 2.55	0.70
Pain	Median (IQR)	0 (0, 17)						
	Above median	14 (28)	–	–		–	–	
	Below median	36 (72)	0.46	0.22, 0.94	**0.035**	0.51	0.26, 1.00	0.050
Dyspnoea	Median (IQR)	33 (0, 33)						
	Above median	9 (18)	–	–		–	–	
	Below median	41 (82)	1.91	0.67, 5.50	0.23	1.31	0.57, 2.97	0.52
Insomnia	Median (IQR)	33 (0, 33)						
	Above median	7 (14)	–	–		–	–	
	Below median	43 (86)	0.59	0.24, 1.44	0.25	0.82	0.34, 1.97	0.66
Appetite loss	Median (IQR)	0 (0, 33)						
	Above median	17 (34)	–	–		–	–	
	Below median	33 (66)	0.60	0.29, 1.21	0.15	0.77	0.40, 1.49	0.44
Constipation	Median (IQR)	0 (0, 0)						
	Above median	6 (12)	–	–		–	–	
	Below median	44 (88)	1.20	0.42, 3.44	0.73	1.45	0.51, 4.11	0.48
Diarrhea	Median (IQR)	0 (0, 33)						
	Above median	19 (39)	–	–		–	–	
	Below median	30 (61)	0.53	0.26, 1.08	0.078	0.89	0.46, 1.73	0.74
	Unknown	1						

TABLE 4 (Continued)

Characteristic		N (%)	OS			PFS		
			HR	95% CI	p value	HR	95% CI	p value
Financial difficulties	Median (IQR)	0 (0, 0)						
	Above median	6 (12)	–	–		–	–	
	Below median	44 (88)	1.31	0.40, 4.31	0.66	1.87	0.57, 6.09	0.30

Note: Significant *p* values (<0.05) are in bold.

Abbreviations: CI, confidence interval; HR, hazard ratio; IQR, interquartile range.

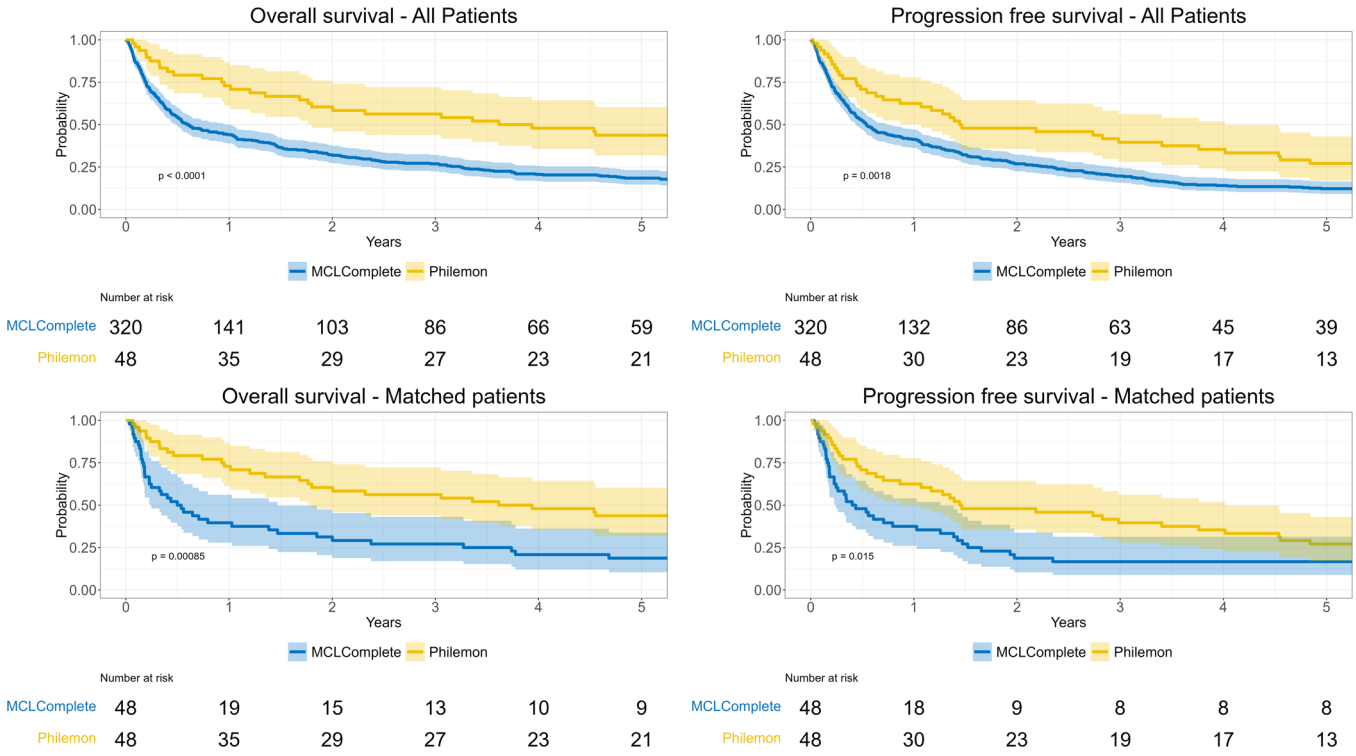

FIGURE 4 **Kaplan–Meier estimates of overall and progression-free survival, comparing the Philemon cohort with IR2 treatment to the population-based MCL*complete* before and after matching.**

Since our study's completion, several regimens combining nonchemotherapeutic agents have shown promising results, demonstrating high response rates and tolerable adverse effects in R/R MCL.[25–27] Simultaneously, ibrutinib has shown superiority over chemotherapy in patients experiencing their first relapse beyond 24 months (POD24).[28] Nonetheless, despite ongoing evaluations of combination therapies, ibrutinib monotherapy remains the standard of care at first relapse.[29,30] Compared to ibrutinib monotherapy, IR2 was associated with a longer median PFS than the median PFS of 12.8 months in a pooled analysis of 370 patients.[31] When stratified by prior lines of treatment, the IR2 regimen had a superior PFS of 32.8 months (IQR: 7.6 to NA) for patients with one prior line of treatment ($n = 25$) (Figure 3), compared to ibrutinib alone ($n = 99$), with a PFS of 25.4 months (95% CI: 17.5–57.5).[30] However, the survival difference decreased with an increasing number of prior treatments. Subsequent studies have demonstrated that combining ibrutinib with rituximab extends the relapse-free period.[32] Beyond ibrutinib and rituximab, recent regimens have introduced additional agents, such as the CD20 antibody obinutuzumab, the BCL-2 inhibitor venetoclax, as well as new generations of BTK inhibitors. While our study demonstrates a superior median PFS compared to ibrutinib alone when given as second-line treatment, it remains unclear whether the IR2 regimen surpasses other combinations, such as venetoclax, with lenalidomide and rituximab (VEN-R2),[25] venetoclax with obinutuzumab and ibrutinib,[26] or acalabrutinib with bendamustine and rituximab,[27] without further randomized trials or extended follow-up.

In the search for novel strategies to address the negative prognostic impact of *TP53* mutations, our study demonstrated a high ORR of 80% in these patients,[15] with a median PFS of 12.8 months and a 1-year PFS of 55% (95% CI: 32, 94). However, the number of patients with *TP53* mutation in our cohort is small, and the observed trend toward worse outcomes suggests that the efficacy should be interpreted with caution. That said, our results are more favorable than *TP53*-mutated patients treated with VEN-R2 ($n = 18$), with ORR of 33% and a 1-year PFS of 33% (95% CI: 17–64).[25] However, preliminary data from the phase 3 SYMPATICO study report a longer PFS compared to our study. Patients with *TP53* mutations ($n = 45$) treated with ibrutinib and venetoklax in SYMPATICO had a median PFS of 20.9 months (95% CI: 12.0–33.1), and the response rates are similar to ours.[33] In addition, an ongoing frontline study investigating

TABLE 5 RMST and differences at 1, 2, and 5 years for all patients and matched patients.

	Time (years)	MCL*complete*	Philemon	RMST difference	*p* value
All patients					
OS	1	0.6 (CI: 0.56–0.64)	0.83 (CI: 0.75–0.92)	0.23 (CI: 0.14–0.33)	<0.01
	2	0.97 (CI: 0.89–1.06)	1.5 (CI: 1.29–1.7)	0.51 (CI: 0.29–0.74)	<0.01
	5	1.69 (CI: 1.49–1.9)	3.05 (CI: 2.47–3.62)	1.32 (CI: 0.71–1.93)	<0.01
PFS	1	0.58 (CI: 0.54–0.63)	0.75 (CI: 0.65–0.85)	0.17 (CI: 0.06–0.28)	<0.01
	2	0.91 (CI: 0.83–1.00)	1.28 (CI: 1.06–1.5)	0.36 (CI: 0.13–0.6)	<0.01
	5	1.44 (CI: 1.26–1.63)	2.42 (CI: 1.85–2.99)	0.98 (CI: 0.38–1.58)	<0.01
Matched patients					
OS	1	0.64 (CI: 0.53–0.75)	0.83 (CI: 0.75–0.92)	0.19 (CI: 0.05–0.34)	<0.01
	2	1.05 (CI: 0.82–1.28)	1.5 (CI: 1.29–1.7)	0.45 (CI: 0.14–0.76)	<0.01
	5	1.78 (CI: 1.24–2.31)	3.05 (CI: 2.48–3.62)	1.27 (CI: 0.49–2.05)	<0.01
PFS	1	0.62 (CI: 0.51–0.74)	0.75 (CI: 0.65–0.85)	0.13 (CI: −0.02 to 0.28)	0.099
	2	0.97 (CI: 0.75–1.19)	1.28 (CI: 1.06–1.5)	0.30 (CI: −0.01 to 0.61)	0.056
	5	1.53 (CI: 1.04–2.02)	2.42 (CI: 1.85–2.99)	0.89 (CI: 0.14–1.64)	0.020

Note: RMST is defined as the area under the survival curve and is utilized to determine the average survival time during a specified time period. The level of significance was evaluated by the Wald test, and 95% confidence interval was determined by pooling standard errors.

Abbreviations: CI, confidence interval; RMST, restricted mean survival time.

TABLE 6 Response after treatment given at the next relapse after the IR2 regimen, both for relapse and primary refractory patients. Thirty-one patients had a relapse after Philemon.

		Response at treatment given at relapse					
Given treatment at relapse	Given treatment, *N* = 23 (%)	CR, *N* = 8 (%)	PR, *N* = 2 (%)	SD, *N* = 1 (%)	PD, *N* = >8 (%)	Unknown response, *N* = 4 (%)	No treatment, *N* = 8
R-Bendamustine	5 (22)	3 (37.5)	1 (50)	0 (0)	1 (12.5)	0 (0)	
Radiotherapy only	5 (22)	0 (0)	1 (50)	1 (100)	1 (12.5)	2 (50)	
Venetoclax-containing regimen	5 (22)	1 (12.5)	0 (0)	0 (0)	3 (37.5)	1 (25)	
R-CHOP with or without radiotherapy	2 (8.7)	2 (25)	0 (0)	0 (0)	0 (0)	0 (0)	
Lenalidomide only	1 (4.3)	0 (0)	0 (0)	0 (0)	1 (12.5)	1 (25)	
Acalabrutinib[a]	1 (4.3)	1 (12.5)	0 (0)	0 (0)	0 (0)	0 (0)	
Ibrutinib[a] and obinutuzumab	1 (4.3)	1 (12.5)	0 (0)	0 (0)	0 (0)	0 (0)	
Temsirolimus	1 (4.3)	0 (0)	0 (0)	0 (0)	1 (12.5)	0 (0)	
Other	2 (8.7)	0 (0)	0 (0)	0 (0)	2 (25)	0 (0)	

[a]Retreatment.

the BTK inhibitor zanubrutinib, combined with venetoclax and obinutuzumab (BOVen), showed an 88% complete remission rate and with a 1-year survival rate of 96% in *TP53*-mutated patients.[34] These regimens, utilizing non-chemotherapeutic agents, including a BTK inhibitor, may represent a promising approach in patients with *TP53* mutations, or serve as a bridge to consolidation with bispecific antibodies or CAR-T cell therapy.

Our study also identified that HRQoL at baseline correlates with OS but not with PFS. Compared to earlier assessments of HRQoL in larger MCL cohorts, the median distribution in the functional and physical scores was similar.[35,36] While it is well-established that both lymphoma and other malignancies can negatively impact HRQoL,[35,37,38] MCL has been noted as a high-risk lymphoma subtype with a comparatively low symptom burden at diagnosis.[36] Given that lower global health status did not correlate with impaired PFS, it is plausible that this measure reflects the broader disease burden. Although comorbidity is known to negatively influence survival in MCL patients,[39] its effects on HRQoL are as yet not completely determined, even though there is evidence that self-reported comorbidity affects HRQoL negatively in lymphoma patients.[37,40] In a clinical context, patients with lower global health status may face a poorer prognosis and could benefit from more intensive supportive care.

In patients treated with the IR2 regimen, six individuals (12%) developed secondary malignancies. Evidence suggests that MCL patients are at increased risk of developing secondary malignancies, particularly melanoma, other skin neoplasms, and hematopoietic or lymphoid cancers.[41] The risk was higher among patients treated with bendamustine, lenalidomide, and ibrutinib, although the exposures for lenalidomide and ibrutinib were small.[41] In the Philemon trial, one patient developed basal cell skin cancer, while two patients over the age of 75 years were diagnosed with prostate cancer and one with rectal cancer. Given the small study population and a median

follow-up of 7.7 years, it is difficult to determine whether the IR2 regimen influences the risk of secondary malignancies. However, assessing long-term risks remains crucial as these treatments become more common and long-term survival rates improve.

Compared to the population-based MCL*complete* cohort, patients treated with the IR2 regimen showed improved survival outcomes, both before and after matching. However, clinical trial participants may be fitter than non-participants and inherently differ on unobserved confounding variables, which may not be fully accounted for by matching methods. Nonetheless, in phase 2 studies for R/R MCL, population-based matching can offer valuable insights, providing a control-arm benchmark for comparison. Worth noting, ibrutinib was reimbursed later in the Nordic countries compared to the United States and other countries. Consequently, its use has been more limited in the Nordic setting. In the MCL*complete* cohort, only six patients had reported previous exposure to ibrutinib. The superior survival observed in patients treated with the IR2 regimen emphasizes the role of ibrutinib and other non-chemotherapeutic agents in the management of R/R MCL. Looking ahead, as the use of ibrutinib and other BTK inhibitors continues to expand, it may be valuable to compare outcomes from the MCL*complete* cohort with those of other BTK inhibitor-containing regimens. Such comparison could provide further insights into how non-chemotherapeutic regimens act in a real-world setting.

In conclusion, our study demonstrates the long-term outcomes of the IR2 regimen in R/R MCL patients and highlights that a lower global health status is associated with worse OS. The superior survival observed for IR2 cohort compared to a matched population-based cohort, as well as durable responses, supports the efficacy of non-chemotherapeutic agents in the treatment of R/R MCL. While the response and PFS rates align with recent studies, this regimen also demonstrated moderate activity in patients with TP53 mutations, although the number of patients are small. However, the high initial response rate, even in TP53 mutated disease, suggests that the IR2 regimen may serve as a bridge to allogeneic stem cell transplantation or CAR-T cell therapy.

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AUTHOR CONTRIBUTIONS

Mats Jerkeman, Ingrid Glimelius, and Elin Forsgren designed the study. Mats Jerkeman and Elin Forsgren designed the case report form. Hans Bentzen, Jon Riise, Jacob Haaber, Annika Pasanen, Hanne Kuitunen, Karin F. Wader, Tarec C. El-Galaly, Martin Hutchings, Ingrid Glimelius, and Mats Jerkeman retrieved follow-up data. Elin Forsgren and Rasmus R. K. Jørgensen did the statistical analysis. Elin Forsgren wrote the manuscript. Mats Jerkeman is responsible for the Philemon trial and MCL*complete*. All authors have read and approved the manuscript.

CLINICAL TRIAL REGISTRATION

The trial was registered on ClinicalTrials.gov (NCT02460276).

CONFLICT OF INTEREST STATEMENT

I. G. received honoraria from Janssen and participated in a real-world data study sponsored by Takeda. M. J. received research support from AbbVie, AstraZeneca, BMS, Janssen, and Roche, and honoraria from AbbVie, AstraZeneca, BMS, Galapagos, Janssen, Kite/Gilead, Lilly, Roche, and Takeda. The other authors had no conflicts of interest to declare.

CONSENT

All patients signed written informed consent at inclusion in Philemon.

DATA AVAILABILITY STATEMENT

To protect patient consent and confidentiality, the dataset presented here is available only upon request to the corresponding author.

ETHICS STATEMENT

The study was approved by national ethics committees in four countries and conducted in accordance with the Declaration of Helsinki and ICH Good Clinical Practice guidelines. For MCL*complete* comparisons, additional approval was obtained from the Regional Ethical Committee in Lund, Sweden (2018/739).

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SUPPORTING INFORMATION

Additional supporting information can be found in the online version of this article.

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